Interim Results from a Phase I/II Clinical Gene Therapy Study for Newly Diagnosed Infants with X-Linked Severe Combined Immunodeficiency Using a Safety-Modified Lentiviral Vector and Targeted Reduced Exposure to Busulfan

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Funding Grants: Lentiviral Gene Therapy for Infants with X-linked Severe Combined Immunodeficiency using Autologous Bone Marrow Stem Cells and Busulfan Conditioning

Public Summary:
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Scientific Abstract:
Early trials of gene therapy for X-linked Severe Combined Immunodeficiency (XSCID) restored T cell immunity in most cases, but did not correct B cell function and carried a high risk of iatrogenic leukemia. The subsequent development of self-inactivating γ-retroviral vectors has enhanced safety, but has not restored B cell function to date. We developed a new approach for XSCID gene therapy that utilizes a safety modified lentiviral (LV) vector (CL20-i4-EF1α-hGC-OPT) together with reduced exposure busulfan (Bu) conditioning for newly diagnosed infants with XSCID. Recently, we reported that the combination of reduced dose Bu used together with our LV vector restored T and B cell function in older XSCID children with declining immune function following haploidentical transplantation (De Ravin SS et al, Sci Transl Med, 2016). Here we report initial results of LVXSCID-ND; a multi-center, phase I/ II safety and efficacy study using our LV vector and dose-adjusted Bu for the first time in newly diagnosed XSCID infants. We enrolled six subjects over the last 12 months (median age of 4.5 months, range: 2-12 months). Purified bone marrow (BM) CD34+ cells were transduced with the CL20-i4-EF1α-hGC-OPT vector generated by a stable producer cell line and then cryopreserved to facilitate central manufacturing for multiple study sites and evaluation of release criteria prior to conditioning. Busulfan was given as two single daily doses to target a total cumulative area-under-the-curve (cAUC) of 22 mg*hr/L (60-90 mg*hr/L = myeloablative cAUC). The median dose of transduced CD34+ cells was 8.06 x 106 cells/kg (range: 4.6 - 11 x 106) and the median vector copy number (VCN) in graft CFU-C was 0.40 copies /cell (range: 0.16 - 0.97). An average Bu cAUC of 22.9 mg*hr/L (range: 20.0 to 24.2) was achieved, which was within 10% of the intended cAUC in all patients. As of July 2017, no severe adverse events related to BM harvest, Bu exposure, or cell infusion have been observed. In the first 5 evaluable cases, complete hematopoietic recovery occurred by 3-4 weeks without any blood product support. Follow-up data from the oldest patient who presented with high levels of maternal T cell engraftment, severe neutropenia requiring G-CSF therapy, CMV viral infection, with a graft VCN of 0.16, and who is now 12 months post therapy, demonstrated delayed and partial T cell reconstitution. Cases 2 and 3 have been followed for nine and six months, respectively and have significantly higher VCNs in peripheral blood (PB) subsets (CD14/15+myeloid cells 0.65, 0.30 copies/cell: CD3+ T cells 2.78, 2.71; CD19+ B cells 1.01, 0.78; and CD56+ NK cells 2.72, 2.11 respectively). Bone marrow aspirates on week 16 yielded VCNs in sorted CD34+ cells of 0.56, 0.50; and BM myeloid CFU-GM of 0.61, 0.24. Rapid T cell reconstitution in cases 2 and 3 resulted in normal numbers of CD3+, CD4+, CD4 naïve, and CD8+ cells with TRECs 626 and 1170 copies per ug DNA 16-20 weeks post therapy. In both cases at 16 weeks, T cell proliferation was 86% and 81% of control, and V-β spectratype scores were normal at 194 and 155. At nine months, case 2 had a normal isohemagglutinin anti-A titer of 1:32 and normal 4-week trough serum immunoglobulins levels (IgG 713 mg/dl, IgM 54 mg/dl, and IgA 16 mg/dl). IVIG supplementation has been discontinued for approximately 3 months before vaccination responses are assessed. Case 4 has been followed for 12 weeks with PB VCNs for CD3+ cells of 1.36 copies/cell, CD19+ 0.58, CD56+ 1.38 and CD14/15+ 0.02. Flow cytometry analysis of PB at 12 weeks shows 4.5% of PB leukocytes are CD3+, with 61% CD4+, 11% CD8+, and a significant fraction expressing a CD45RA+, RO- naive phenotype at this early time point. Cases 5 and 6 are still too early to evaluate for immune phenotype and function. Preliminary vector insertion site analysis shows highly polyclonal marking patterns in case 2 with 11,000 insertion sites in CD3+ cells, 5049 sites in CD19+ cells, 756 sites in BM myeloid CFU-C without any evidence of clonal dominance. In summary, gene therapy for newly diagnosed XSCID patients using a LV vector with targeted reduced exposure Bu conditioning is well tolerated and results in rapid T cell reconstitution in most cases. Efficient vector marking in bone marrow CD34+ cells, myeloid cells, and B cells indicate that this approach will likely provide broad

immune reconstitution rather than restricted T cell correction seen in past trials using γ-retroviral vectors with no Bu.
